Attorney Docket No. 9448-51 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Thomas W. Leonard
Application No.: 10/821,278
Filed: April 8, 2004
Confirmation No.: 1153
Group Art Unit 1617
Examiner: Sahar Javanmard
For: **METHODS OF ADMINISTERING ESTROGENS AND PROGESTINS**

Date: December 15, 2009

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APPELLANT'S BRIEF ON APPEAL UNDER 37 C.F.R. § 1.192

Sir:

This Appeal Brief is filed pursuant to the Notice of Appeal to the Board of Patent Appeals and Interferences ("the Notice") filed on June 2, 2009.

REAL PARTY OF INTEREST

The real party of interest is Barr Laboratories, Inc., the assignee of this application.

RELATED APPEALS AND INTERFERENCES

Appellants are aware of no appeals or interferences that would be affected by the present appeal.

STATUS OF ALL CLAIMS

As of the filing date of this Appeal Brief, claims 10–16, 19–23 and 29 are pending in the present application. Claims 10–16 stand finally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1–7 of U.S. Patent No. 7,427,609 B2 to Leonard et al. ("Leonard et al."). Claim 1 stands rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 6 of co-

pending U.S. Application Serial No. 10/356,242. Claims 10–16, 19–23 and 29 stand finally rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Application Publication No. 2001/0034340 ("Pickar") in view of U.S. Patent No. 5,798,347 ("Labrie"), U.S. Patent No. 4,381,298 ("Coulson"), Prestwood et al. (2000) *J. Clin. Endocrinol. Metab.* 85:4462–4469 ("Prestwood et al."), and Utian et al. (1999) *A. J Obstet. Gynecol.* 181:71–79 ("Utian et al."). The specifics of these rejections are set forth in the Final Office Action ("the Final Action") mailed March 2, 2009. Claims 1–9, 17, 18, 24–28, 30 and 31 are canceled.

STATUS OF AMENDMENTS

All amendments made by Appellants during prosecution have been entered as indicated in the Final Action.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention, as set forth in independent claims 10 and 29, and dependent claims 11–16 and 19–23, is directed toward methods of treating vasomotor symptoms comprising administering a therapeutic amount of an estrogenic compound and a therapeutic amount of a progestational agent.

Independent claim 10 is directed toward a method of treating vasomotor symptoms comprising: administering a first dose of a therapeutic amount of an estrogenic compound to a subject; administering a second dose of a therapeutic amount of an estrogenic compound at a later period of time, said second dose comprising a lower dosage of a therapeutic amount of an estrogenic compound than said first dosage; and administering a therapeutic amount of a progestational agent of less than 20 mg as supported at paragraph [00013] of the specification.

Independent claim 29 is directed toward a method for treating a patient afflicted with vasomotor symptoms, comprising administering an estrogenic compound to said patient for at least two cycles of a cyclical dosing schedule, wherein the first cycle comprises a dosing period of 4 to 12 weeks, in which the estrogenic compound is administered daily, at a dose of 0.625 to 1.5 mg/day as supported at paragraph [00022] of the specification, followed by a second cycle

comprising a dosing period that can last for an indeterminate period of time in which an estrogenic compound is administered daily, at a dose of 0.05 to 0.625 mg/day as supported at paragraphs [00022] and [00056] of the specification, and by administering megestrol acetate daily at a dose of 6 mg/day as support at paragraphs [00071] and [00073] of the specification.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

As an initial matter, Appellants believe that the grounds for the double patenting rejections as set forth in the Final Action have been addressed in view of the Terminal Disclaimers to U.S. Patent No. 7,427,609 B2 and U.S. Application Serial No. 10/356,242 filed with the Notice on June 2, 2009. As such, the grounds of rejection to be reviewed on appeal are whether claims 10–16, 19–23 and 29 are unpatentable under 35 U.S.C. § 103(a) over Pickar in view of Labrie, Coulson, Prestwood et al., and Utian et al. as set forth in the Final Action mailed March 2, 2009.

ARGUMENT

I. Legal Standard for Obviousness

Claims 10–16, 19–23 and 29 are rejected under 35 U.S.C. § 103(a) over Pickar in view of Labrie, Coulson, Prestwood et al., and Utian et al. A determination under § 103 that an invention would have been obvious to someone of ordinary skill in the art is a conclusion of law based on fact. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1593, 1 U.S.P.Q.2d 1593 (Fed. Cir. 1987), *cert. denied*, 107 S.Ct. 2187. After the involved facts are determined, the decision maker must then make the legal determination of whether the claimed invention as a whole would have been obvious to a person having ordinary skill in the art at the time the invention was made. *Id.* at 1596. The United States Patent and Trademark Office ("USPTO") has the initial burden under § 103 to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

As stated in the recently published Examination Guidelines for Determining Obviousness, "the Supreme Court reaffirmed the familiar framework for determining

obviousness as set forth in *Graham v. John Deere Co....*" (Examination Guidelines for Determining Obviousness Under 35 U.S.C § 103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* Federal Register Vol. 72, No. 195, 57526-57535, 57526). Hence, and as long established under that framework, to establish a *prima facie* case of obviousness, three requirements must be satisfied (M.P.E.P. § 2143). First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. *In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the proposed modification or combination of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Third, the prior art reference or combination of references must teach or suggest all of the limitations of the claims. *See In re Wilson* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art").

As discussed above, the prior art reference or references when combined must teach or suggest *all* the recitations of the claims, and there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. M.P.E.P. § 2143. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. M.P.E.P. § 2143.01, citing *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). As emphasized by the Court of Appeals for the Federal Circuit, to support combining references, evidence of a suggestion, teaching, or motivation to combine must be **clear and particular**, and this requirement for clear and particular evidence is not met by broad and conclusory statements about the teachings of references. *In re Dembiczak*, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). In an even more recent decision, the Court of Appeals for the Federal Circuit has stated that, to support combining or modifying references, there must be **particular** evidence from the prior art

as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed. *In re Kotzab*, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000).

II. Claims 10–16, 19–23 and 29 are patentable over Pickar in view of Labrie, Coulson, Prestwood et al., and Utian et al.

The Examiner submits that it would have been obvious to one of ordinary skill at the time the invention was made to treat vasomotor symptoms according to the method as set forth in claims 10–16, 19–23 and 29 as set forth at page 10, line 12 through page 11, line 6 of the Final Action. The Examiner relies on the disclosures of Prestwood et al. and Utian et al. to provide motivation to administer the dosage in a first and lower second dosage or even a lower third dosage based on lower frequency of side effects at the lower dosages and the disclosures of Pickar to suggest that the dosage of a patient may need to be adjusted (either up or down) to achieve the desired effect during the middle of a treatment period. Appellants respectfully disagree.

As the primary reference cited, the Examiner points out that Pickar et al. disclose a composition comprising preferably conjugated estrogens for estrogen replacement therapy, and that Pickar et al. disclose that "[t]he dosage of a patient may need to be adjusted (either up or down) to achieve the desired effect during the middle of a treatment period." (paragraph [0022]). However, Pickar et al. fail to specifically teach, by the admission of the Examiner, "[a] second dose after therapy of the vasomotor symptoms has been effectively established," wherein "the second dose of an estrogenic compound is administered between 2 weeks and 12 weeks after the first dose of an estrogenic compound," "the second dose is administered between 4 weeks and 8 weeks after the first dose of an estrogenic compound," "the first predetermined time period for said first dose of an estrogenic compound is at least twelve weeks before the administration of said second dose of an estrogenic compound," or "the first predetermined time period for said fist dose of an estrogenic compound is at least four to eight weeks before the administration of said second dose of an estrogenic compound." Appellant further point out that Pickar et al. also

fail to explicitly teach or suggest a method of treating vasomotor symptoms wherein the second dose of an estrogenic compound is lower than the first dose.

The present invention sets forth a method for treating vasomotor symptoms comprising administration of a fist dose of an estrogenic compound, followed by administration of a second dose of an estrogenic compound at a later time period second dose comprising a lower dosage of said therapeutic amount of an estrogenic compound than said first dose, and administering a therapeutic amount of a progestational agent of less than 20 mg. When considering whether the prior art teaches the invention, the entirety of the disclosures in prior art must be considered.

On pages 7–8 of the Final Action, the Examiner points out that Pickar et al. note that "[i]t is preferred that the dosage of PREMARIN is about 0.625 mg per day or less, and is more preferred that the dosage of PREMARIN is either about 0.45 mg per day or about 0.3 mg per day." These ranges are less than the ranges envisioned in the first dose of the method of the present invention. The disclosures of Utian et al. suggest that based on their studies, " [a] logical approach is to initiate treatment with a low dose of estradiol, which is more likely to provide an acceptable level of relief from vasomotor symptoms while minimizing the signs of hyperestrogenism." (p. 78 col. 2 lines 17–20). The preferred amounts as indicated by Pickar et al. and by the disclosures of Utian et al. suggest that treatment be initiated at low doses of estrogenic compounds. The dose of estrogenic compounds discussed by Pickar and Utian et al. is lower than those envisioned for the first dose in the method of the present invention. As such, the disclosures of Pickar et al. and Utian et al. teach away from a high first dose of an estrogenic compound in the method of the present invention.

In contrast, while the disclosures of Pickar et al. and Utian et al. suggest the advantages of initiating estrogen replacement therapy at low doses of an estrogenic compound, the disclosures of Prestwood et al. point out that, "[i]n younger postmenopausal women, the use of lower doses of estrogen may not be as effective in preventing bone loss." (p. 4467 col. 1 lines 8–10). However, as with the disclosures of Pickar et al. and Utian et al., the disclosures of Prestwood et al. do not explicitly disclose or suggest a method of treating vasomotor symptoms wherein the second dose of an estrogenic compound is lower than the first dose. The disclosures of Labrie and Coulson are relied on so far as to only show that medroxyprogesterone acetate is a

progestin and an androgen, respectively, and do not contribute further to the deficiencies in the disclosures of Pickar et al., Utian et al. and Prestwood et al. in explicitly describing or suggesting all the elements of that which is claimed.

In view of the foregoing, Appellants respectfully submit that the disclosures of Pickar et al. in view of Labrie, Coulson, Prestwood et al., and Utian et al. do not teach all the elements of the method as instantly claimed. Furthermore, Appellants submit that the disclosures of Pickar et al. in view of Labrie, Coulson, Prestwood et al., and Utian et al., when taken as a whole, do not provide the teaching, motivation or suggestion, individually or in combination, in order to arrive at the method of the invention. As such, Appellants present that claims 10–16, 19–23 and 29 are directed toward patentable subject matter, and respectfully request that the instant rejection be reversed on appeal.

CONCLUSION

In light of the entire record and the above discussion, Appellants respectfully submit that the instant claims are patentable over the cited prior art. Accordingly, Appellants respectfully request reversal of the rejection of the instant claims and that this case be passed to issuance.

A petition for a five-month extension of time is required with the filing of this paper. Said petition is filed concurrently herewith. Applicants hereby authorize the Commissioner to charge Deposit Account No. 50-0220 in the amount of $2,350.00 as fee for the extension. Applicants believe this amount to be correct; however, the Commissioner is hereby authorized to charge any deficiency or credit any refund to Deposit Account No. 50-0220.

Respectfully submitted,

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CERTIFICATION OF ELECTRONIC TRANSMISSION
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Cara L. Rose

CLAIMS APPENDIX

APPENDIX A presents the listing of the claims at issue as finally rejected in the Final Action.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.

APPENDIX A

Listing of Claims
U.S. Patent Application Serial No. 10/821,278
Leonard et al., Filing Date: April 8, 2004

1–9. (Canceled)

10. (Previously presented) A method of treating vasomotor symptoms comprising:

administering a first dose of a therapeutic amount of an estrogenic compound to a subject;

administering a second dose of a therapeutic amount of an estrogenic compound at a later time period to the subject, said second dose comprising a lower dosage of said therapeutic amount of an estrogenic compound than said first dose; and

administering a therapeutic amount of a progestational agent of less than 20 mg.

11. (Original) The method according to claim 10, wherein said progestational agent is selected from the group consisting of megestrol acetate, laevo-norgestrel, dl-norgestrel, norethindrone (norethisterone), norethindrone (norethisterone) acetate, ethynodiol diacetate, dydrogesterone, medroxyprogesterone acetate, norethynodrel, allylestrenol, lynoestrenol, quingestanol acetate, medrogestone, norgestrienone, dimethisterone, ethisterone, and cyproterone acetate.

12. (Original) The method according to claim 10, further comprising administering an androgen compound in a daily dose.

13. (Original) The method according to claim 11, wherein said megestrol acetate is continuously and uninterruptedly administered to said subject.

14. (Original) The method according to claim 11, wherein said megestrol acetate is administered in doses ranging from 1 mg to less than 20 mg.

15. (Original) The method according to claim 10, wherein the estrogenic compound comprises a mixture of estrogenic compounds, wherein said mixture comprises salts of conjugated estrone, conjugated equilin, conjugated $\Delta^{8,9}$-dehydroestrone, conjugated 17α-estradiol, conjugated 17α-dihydroequilin, conjugated 17β-dihydroequilin, conjugated 17β-estradiol, conjugated equilenin, conjugated 17α-dihydroequilenin, and conjugated 17β-dihydroequilenin.

16. (Original) The method according to claim 10, the estrogenic compound comprises a mixture of estrogenic compounds wherein said conjugated estrogens is selected from the group consisting of the sodium sulfate esters of estrone, equilin, 17α-dihydroequilin, 17β-dihydroequilin and 17α-estradiol.

17 and 18. (Canceled)

19. (Previously presented) The method according to claim 10, wherein said second dose of an estrogenic compound is administered between 2 weeks and 12 weeks after the first dose of an estrogenic compound.

20. (Previously presented) The method according to claim 10, wherein said second dose of an estrogenic compound is administered between 4 weeks and 8 weeks after the first dose of an estrogenic compound.

21. (Previously presented) The method according to claim 10, wherein said vasomotor symptoms are selected from the group of hot flashes, cold flashes, night sweats, day sweats, dry vagina, dry hair and skin, insomnia, bladder problems and moodiness.

22. (Previously presented) The method according claim 10, wherein said first dose is continuously and uninterruptedly administered to said subject for a predetermined period of time and then said second dose is continuously and uninterruptedly administered to said subject.

23. (Previously presented) The method according to claim 10 further comprising:

administering a third dose of a therapeutic amount of an estrogenic compound at a later time period to the subject than that of said second dose, said third dose comprising a lower dosage of said therapeutic amount of an estrogenic compound than said second dose.

24–28. (Canceled.)

29. (Previously presented) A method for treating a patient afflicted with vasomotor symptoms, comprising administering an estrogenic compound to said patient for at least two cycles of a cyclical dosing schedule, wherein the first cycle comprises a dosing period of 4 to 12 weeks, in which the estrogenic compound is administered daily, at a dose of 0.625 to 1.5 mg/day, followed by a second cycle comprising a dosing period that can last for an indeterminate period of time in which an estrogenic compound is administered daily, at a dose of 0.05 to 0.625 mg/day and by administering megestrol acetate daily at a dose of 6 mg/day.

30–31. (Canceled.)